REMARKS

Status of the Claims

Claims 1, 12, 21-23, 31-34, 37-42, 44-48, 50-55, 58-65 and 67-72 were currently pending. Claims 1, 23, 31, 39, 45, 50, 60, and 68 have been amended to recite "a second peptidyl fragment comprising the amino acid sequence of SEQ ID NO:2 or comprising the amino acid sequence of SEQ ID NO:2 having no more than one conservative amino acid substitution, wherein the substituted peptidyl fragment retains at least 90% of the 3'(2'),5'-bisphosphonate activity of SEQ ID NO:2." Support for the amendments to the claims can be found, *inter alia*, at paragraphs **[0018]**, **[0040]**, and **[0041]**. No new matter is added by the amendments. The remaining claims have not been further amended. After entry of the amendment, claims 1, 12, 21-23, 31-34, 37-42, 44-48, 50-55, 58-65 and 67-72 will be pending.

This application pertains to compositions and assays for sodium and lithium ions using ion-sensitive enzymes. In particular, the ion-sensitive enzyme is a chimeric protein comprising a specific bacterial leader sequence, a 3'(2'), 5"-bisphosphate nucleotidase of SEQ ID NO:2 (or having no more than one conservative amino acid substitution and at least 90% of the bisphosphonate activity of SEQ ID NO:2); and a fragment comprising the sequence of SEQ ID NO:3. The bisphosphonate activity is the activity of forming inorganic phosphate and AMP from adenosine 5' biphosphate. (See paragraph **[0043]** of the specification).

The outstanding issues are written description and enablement. The claims were not rejected over the prior art.

Entry of the amendment and reconsideration in view of the following comments is respectfully requested. With respect to all amendments, Applicants have not dedicated or abandoned any unclaimed subject matter and moreover have not acquiesced to any rejections and/or objections made by the Patent Office. Applicants expressly reserve the right to pursue prosecution of any presently excluded subject matter or claim embodiments in one or more future continuation and/or divisional application(s).

Claim 23

Claim 23 was not rejected or objected to in the previous (12.16.2009) Office Action, and accordingly, Applicants submit that this claim should have been indicated as allowable.

Rejection Under 35 U.S.C. §112, first paragraph, written description

Claims 1, 12, 21, 22, 31-34, 37-42, 44-48, 50-55, 58-65, 67-72 were rejected under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The Office has taken the position that the claims do not place any limitation upon the number of conservative amino acid substitutions that may be made to SEQ ID NO:2. (12.16.2009 OA at page 5.) Accordingly, the Office asserts that the claimed chimeric proteins comprise an enormous number of species.

Applicants have amended the claims to recite that the polypeptides comprise "a second peptidyl fragment comprising the amino acid sequence of SEQ ID NO:2 or comprising the amino acid sequence of SEQ ID NO:2 having no more than one conservative amino acid substitution, wherein the substituted peptidyl fragment retains at least 90% of the 3'(2'),5'-bisphosphonate activity of SEQ ID NO:2."

In view of the amendments, it is clear that the pending claims do not encompass polypeptides having more than one conservative substitution.

Applicants incorporate in their entirety its previous arguments relating to written description, and particularly its arguments filed in response to the June 9, 2010 office action. Specifically, Applicants assert that conservative amino acid substitutions of amino acid sequences were well-known in the art, and were fully described in the specification at paragraph **[0018]**. A person of ordinary skill in the art could empirically replace not more than one amino acid in SEQ ID

NO:2 with a conservative amino acid substitution, and test the resultant peptide to determine whether it has retained the requisite 90% of the 3'(2'),5'-bisphosphonate activity of SEQ ID NO:2. Thus, the pending claims place a numerical limitations upon the number of conservative amino acid substitutions that may be made to SEQ ID NO:2.

In light of the foregoing discussion and the amendments, Applicants respectfully submit that the specification, combined with the knowledge in the art at the time of the present invention, provides sufficient disclosure to convey to a person skilled in the art that Applicants were in possession of the claimed invention. Accordingly, Applicants respectfully submit that this written description rejection under 35 U.S.C. § 112, first paragraph may properly be withdrawn.

Rejection Under 35 U.S.C. §112, first paragraph, enablement

Claims 1, 12, 21, 22, 31-34, 37-42, 44-48, 50-55, 58-65 and 67-72 stand rejected under 35 U.S.C. §112, first paragraph as allegedly failing to meet the enablement requirement.

The Office has taken the position that because any unlimited number of amino acid substitutions may be made in the claimed peptide, that the specification does not provide the requisite level of guidance.

Applicants traverse this rejection. Practicing the amended claims does not require undue experimentation.

Claim 1 is directed to an isolated chimeric protein having the enzymatic activity of a nucleotidase, which chimeric protein comprises, from N-terminus to C-terminus, a first peptidyl fragment comprising a bacterial leader sequence comprising an amino acid sequence as set forth in SEQ ID NO:1; a second peptidyl fragment comprising the amino acid sequence of SEQ ID NO:2 or comprising the amino acid sequence of SEQ ID NO:2 having not more than one conservative amino acid substitution, wherein the substituted peptidyl fragment retains at least 90% of the 3'(2'),5'-bisphosphonate activity of SEQ ID NO:2.; and a third peptidyl fragment comprising an amino acid

sequence as set forth in SEQ ID NO:3. The other pending claims all contains this same claim language.

Applicants have amended the claims to recite that the polypeptides comprise "a second peptidyl fragment comprising the amino acid sequence of SEQ ID NO:2 or comprising the amino acid sequence of SEQ ID NO:2 having no more than one conservative amino acid substitution, wherein the substituted peptidyl fragment retains at least 90% of the 3'(2'),5'-bisphosphonate activity of SEQ ID NO:2."

In view of the amendments, it is clear that the pending claims do not encompass polypeptides having more than one conservative substitution.

Applicants incorporate in their entirety its previous arguments relating to enablement, and particularly its arguments filed in response to the June 9, 2010 office action. Notably, the pending claims place a numerical limitations upon the number of conservative amino acid substitutions that may be made to SEQ ID NO:2. The pending claims do not recite an unlimited number of amino acid substitutions. A person of ordinary skill in the art could empirically replace not more than one amino acid in SEQ ID NO:2 with a conservative amino acid substitution, and test the resultant peptide to determine whether it has retained the requisite 90% of the 3'(2'),5'-bisphosphonate activity of SEQ ID NO:2. It would not take undue experimentation to arrive at this number of SEQ ID NO:2 mutants.

In light of the foregoing discussion and the claim amendments, Applicants respectfully submit that the specification, combined with the knowledge in the art at the time of the present invention, provides reasonable guidance to the skilled artisan regarding how to make and use the invention, including providing sufficient guidance on protein structure and sufficient guidance on methods for designing variant proteins containing not more than one conservative amino acid substitution and having a desired activity. Accordingly, Applicants respectfully submit that this enablement rejection under 35 U.S.C. § 112, first paragraph may properly be withdrawn.

CONCLUSIONS

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to withdraw the outstanding rejection of the claims and to pass this application to issue. If it is determined that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number given below.

In the event the U.S. Patent and Trademark office determines that an extension and/or other relief is required, applicant petitions for any required relief including extensions of time and authorizes the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to Deposit Account No. 03-1952 referencing docket no. 466992001100. However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

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